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**D E C I S I O N**  
**of 22 March 2000**

**Case Number:** T 1089/96 - 3.3.2

**Application Number:** 90106397.4

**Publication Number:** 0391369

**IPC:** A61K 9/107

**Language of the proceedings:** EN

**Title of invention:**  
Medicinal emulsions

**Patentee:**  
YISSUM RESEARCH DEVELOPMENT COMPANY OF THE HEBREW UNIVERSITY  
OF JERUSALEM

**Opponent:**  
B. Braun Melsungen Aktiengesellschaft  
Pharmacia & Upjohn

**Headword:**  
Emulsions/YISSUM RESEARCH DEVELOPMENT

**Relevant legal provisions:**  
EPC Art. 56

**Keyword:**  
"Main, first, second auxiliary request - inventive step - no"  
"Claim 1 encompasses an obvious embodiment - third auxiliary  
request"  
"Inventive step - yes - improved stability not obvious"

**Decisions cited:**  
-

**Catchword:**

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Boards of Appeal

Chambres de recours

Case Number: T 1089/96 - 3.3.2

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.2**  
**of 22 March 2000**

**Appellant/other party:** B. Braun Melsungen Aktiengesellschaft  
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**Respondent:** YISSUM RESEARCH DEVELOPMENT COMPANY OF THE  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 14 October 1996  
rejecting the opposition filed against European  
patent No. 0 391 369 pursuant to Article 102(2)  
EPC.

**Composition of the Board:**

**Chairman:** U. Oswald

**Members:** J. Riolo  
C. Rennie-Smith

## Summary of Facts and Submissions

I. European Patent No. 0 391 369 based on application No. 90 106 397.4 was granted on the basis of 25 claims for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL SE and 23 claims for the Contracting States ES and GR.

Independent claim 1 of the set of claims for the Contracting States other than ES and GR as granted read as follows:

"1. A pharmaceutical composition comprising an effective amount of a hydrophobic drug and a pharmaceutically acceptable carrier being an oil-in-water type emulsion comprising  
(i) about 3-50% (w/v) of an oily carrier consisting of medium chain triglyceride (MCT) oil, optionally in combination with vegetable oil;  
(ii) about 0.05-20% (w/v) of phospholipids;  
(iii) about 0.03-10% (w/v) of a non-ionic surfactant;  
and  
(iv) about 0.05-10% (w/v) of an ionic surfactant selected from bile-duct surface active agent, cholic acid and deoxycholic acid, and their surface active derivatives and salts."

The independent claim 1 of the set of claims for ES and GR as granted read as follows:

"1. A process for the preparation of a composition of the oil-in-water type emulsion comprising an effective amount of a hydrophobic drug, about 3-50% (w/v) of an oily carrier consisting of medium chain triglyceride

(MCT) oil, optionally in combination with vegetable oil, about 0.05%-20% (w/v) of phospholipid, about 0.03-10% (w/v) of a non-ionic surfactant, and about 0.05-10% (w/v) of an ionic surfactant selected from bile-duct surface active agents, cholic acid and deoxycholic acid, and their surface active derivatives and salts, which process comprises:

- (a) preparing a liposome mixture comprising the phospholipids, the non-ionic surfactant, the said ionic surfactant, and where the drug has a poor oil solubility, also comprising said drug;
- (b) preparing an oily mixture comprising said oily carrier, and where the drug is lipophilic, also comprising said drug;
- (c) mixing said liposome mixture with said oily mixture, whereby said emulsion is obtained."

II. Notices of opposition were filed against the granted patent by two parties (hereinafter referred to as the appellant and the opponent 02).

The patent was opposed under Article 100(a) EPC for lack of inventive step.

The following documents were cited inter alia during the proceedings.

- (1) EP-A-0 143 305
- (2) The Journal of Hospital Pharmacy, 1974, pp 149-171
- (3) EP-A-0 296 845

III. The decision of the Opposition Division of 25 September

1996, posted on 14 October 1996 rejected the oppositions under Article 102(2) EPC.

The Opposition Division took the view that the patent in suit met the requirements of Articles 52(1) and 56 EPC.

It considered that the subject-matter of claim 1 was inventive over the combination of document (1) with document (2) as well as over the combination of document (3) with (2).

The Opposition Division found that, although the emulsifiers of the patent in suit were disclosed in the review Article (2), the skilled person had no incentive to combine its teaching with that of documents (1) or (3) as the effect on the stability of the emulsions achieved by the presence of these emulsifiers could not be foreseen.

Further combinations presented by the opponent O2 were also rejected by the Opposition Division.

- IV. The appellant (opponent O1) lodged an appeal against the said decision. By a letter dated 7 March 2000 the appellant informed the Board of its decision to withdraw its request for oral proceedings.
- V. Oral proceedings were held before the Board on 22 March 2000 during which a main request and auxiliary requests 1 to 3 were filed by the respondent (patentee).

Claim 1 of the set of claims for the Contracting States

other than ES and GR of these newly filed requests corresponded to claim 1 as granted with the following amendments:

- in the main request the sentence "wherein the mean oily droplet diameter is about 0.1 - 0.15  $\mu\text{m}$ " was added at the end of the claim 1 as granted.
- in the first auxiliary request, the sentence "wherein the mean oily droplet diameter is below 0.2  $\mu\text{m}$ " was added at the end of the claim 1 as granted. In addition, the hydrophobic drug is defined by adding "selected from the group consisting of hydrophobic or lipophilic antibiotics or narcotic drugs, hydrophobic benzodiazepines, non-steroidal anti-inflammatory lipophilic drugs, lipophilic steroids, lipophilic azoles, lipophilic polypeptides, lipophilic steroids, lipophilic cephalosporines and dimercaptol" in the claim after the terms "a hydrophobic drug".
- in the second auxiliary request, beside the same amendment as in the main request, the drug was defined by adding "selected from the group consisting of amphotericin B, morphine-base, diazepam, fluphenazine deconate, lorazepam, piroxicam, indomethacin, progesterone, testosterone propionate, miconazole, clotrimazole, cyclosporine, deoxycortone, calciferol, cephalosporine and dimercaptol" in the claim after the terms "a hydrophobic drug".
- in the third auxiliary request, beside the same



amendment as in the main request, the terms "a hydrophobic drug" was replaced by "a hydrophobic benzodiazepine" and the terms " bile-duct surface active" were deleted.

Claim 1 of the set of claims for the Contracting States ES and GR of these newly filed requests corresponded to claim 1 as granted with the same amendments as above.

The wording of claim 1 of the third request of this set of claims was moreover adapted accordingly and read:

"1. A process for the preparation of a composition of the oil-in-water type emulsion comprising an effective amount of a hydrophobic benzodiazepine, about 3-50% (w/v) of an oily carrier consisting of medium chain triglyceride (MCT) oil, optionally in combination with vegetable oil, about 0.05%-20% (w/v) of phospholipid, about 0.03-10% (w/v) of a non-ionic surfactant, and about 0.05-10% (w/v) of an ionic surfactant selected from cholic acid and deoxycholic acid, and their surface active derivatives and salts wherein the mean oily droplet diameter is about 0,1 to 0,15  $\mu\text{m}$ , which process comprises:

- (a) preparing a liposome mixture comprising the phospholipids, the non-ionic surfactant, the said ionic surfactant;
- (b) preparing an oily mixture comprising said oily carrier, and also comprising said drug;
- (c) mixing said liposome mixture with said oily mixture, whereby said emulsion is obtained."

This process claim is moreover identical in substance to the process claim of the third auxiliary request of

the set of claims for the Contracting States other than ES and GR.

VI. The submissions of the appellant in the written procedure can be summarized as follows:

It considered document (1) as the closest state of the art and defined the problem to be solved over this document as the provision of a further emulsion containing the hydrophobic drug amphotericin B.

It argued that, having regard to the teaching in document (2), the skilled person would use the recommended combination of a phospholipid and a non-ionic emulsifier in order to stabilise a hydrophobic drug emulsion. He would also use sodium-desoxycholate as solvent in the case of the hydrophobic drug amphotericin B as document (3) disclosed it as a good solvent for that drug.

It therefore concluded that the subject-matter of claim 1 of the patent in suit, as far as heat sensitive drugs such as amphotericin B were concerned, resulted from an obvious combination of the teachings of documents (1) with (2) and (3).

The opponent O2 took no part in either the written or the oral appeal proceedings.

VII. The respondent's arguments submitted both in the written procedure and at the oral proceedings can be summarized as follows:

In the respondent's view the subject-matter of claim 1

of the patent in suit involved an inventive step because there were no hints in the cited documents that the combination of an oily carrier of medium chain triglyceride with the three emulsifiers according to claim 1 of the patent in suit resulted in emulsions having improved stability as demonstrated in the patent in suit for the hydrophobic drug diazepam. Diazepam was regarded as representing the whole group of hydrophobic drugs.

It further stressed the point that the simple fact that all features of a claim could be individually found in two or more documents did not render it automatically obvious.

VIII. The appellant requested that the decision under appeal be set aside and that the European patent n° 391 369 be revoked.

The respondent requested that the decision under appeal be set aside and that the patent be maintained on the basis of the Main Request or alternatively on the basis of auxiliary Requests 1-3 as submitted during the oral proceedings.

### **Reasons for the Decision**

1. The appeal is admissible.
2. *Article 123 EPC*

The Board sees no objections on the basis of Article 123(2) and (3) EPC to the main or first, second

and third auxiliary requests since the claims are adequately supported by the original disclosure and do not extend the protection conferred when compared to the claims as granted.

3. *Novelty*

Novelty of the subject-matter of the claims of the patent in suit was acknowledged by the Opposition Division, which examined it of its own motion. The Board sees no reason to object to these findings. Moreover, the appellant did not object under Article 54 EPC.

4. *Inventive step*

4.1 Main request

4.1.1 The patent in suit concerns pharmaceutical compositions of hydrophobic drugs, such as amphotericin B and diazepam, being in the form of oil-in-water emulsions which remain stable during prolonged storage (page 2, lines 3 to 6, page 4, lines 6 to 13).

Document (3) relates also to pharmaceutical compositions of hydrophobic drugs, such as amphotericin B, being in the form of oil-in-water emulsions which are described as being stable over prolonged storage.

The Board therefore regards document (3) as the closest prior art (column 1, line 49 to column 2, line 14).

4.1.2 Examples 1 and 3 of this document describe oil-in-water emulsion systems containing the hydrophobic drug

amphotericin B in an oily carrier and a phospholipid (lecithin) as emulsifier.

Medium chain triglycerides (MCT) are mentioned as oily carries as an alternative to vegetable oils in an amount of 5 to 50% and non-ionic surfactant as alternative to phospholipid emulsifiers in an amount of 0.5 to 10% in the description (column 3, lines 19 to 23 and column 4, lines 3 to 12). The surfactant sodium deoxycholate is also disclosed as an ingredient for Amphotericin B preparations in the introduction of the document (column 1, lines 4 to 8).

Examples 4 mentions that a change of less than 10% change in mean diameter over at least 10 weeks was noted with the emulsions of the document. Moreover, it can be derived from example 5 and figure 4 that a stability of at least 170 days for the particle sizes of the emulsions of the document of a mean size of 200-350 nm (0.2-0.35  $\mu\text{m}$ ) was achieved.

Since example 9 and figure 4 of the patent in suit show a stability of at least 3 months for the emulsions of the drug amphotericin B, the problem to be solved as against document (3), in as far as the drug amphotericin B is concerned, can only be seen as the provision of a further composition of the oil-in-water type emulsion which remains stable during prolonged storage.

4.1.3 This problem is solved by the subject-matter of claim 1 and, in the light of working example 9 and figure 4 of the patent in suit, the Board is satisfied that the problem has been solved.

4.1.4 Thus, the question to be answered is whether the proposed solution, ie where the use of a medium chain triglyceride oil carrier with an emulsifier combination of phospholipids, non-ionic surfactant, and bile-duct surface active agent, cholic acid or deoxycholic acid in the amount as indicated in claim 1 as emulsifier, was obvious to the skilled person in the light of the prior art.

The Board notes that document (3) discloses the use of a medium chain triglyceride oil carrier for the preparation of the emulsions and also discloses the three emulsifiers of claim 1 of the patent in suit as being suitable for use in combination with amphotericin B. The Board agrees with the respondent that this document is silent about the use of a **combination** of each of these emulsifiers for the preparation of the oil-in-water emulsions.

However, having regard to document (2), a review article referring to fat emulsions for intravenous application, the skilled person is clearly taught that the use of a combination of phospholipids and non-ionic surfactants improves the stability of oil-in-water emulsions (page 151, left column, lines 12 to 16).

Moreover, as sodium deoxycholate is a well-know solubilising agent for amphotericin B the Board cannot see anything preventing the skilled person from using

some of this usual ingredient in combination with the two other emulsifiers.

The Board notes that both the amounts of emulsifier used in (3) and the value of the mean oily droplet diameter are analogous to those of claim 1 of the patent in suit.

Therefore, the Board is satisfied that the skilled person faced with the problem of providing an **alternative oil-in-water type emulsion for amphotericin B** would arrive at the combination of the three emulsifiers according to claim 1 of the contested patent without an inventive step.

4.1.5 The Board cannot share the opinion of the respondent that (i) the stability of at least three months for amphotericin B mentioned in the patent in suit did not imply that this stability was limited to 3 months, (ii) that, having regard to the 14 months stability demonstrated for diazepam in example 4 of the contested patent, it was clear that the unique combination of emulsifiers according to claim 1 provided for emulsions of hydrophobic drugs which were more stable than the prior art hydrophobic drug containing emulsions and (iii) that the stability effect could not be foreseen.

4.1.6 It is indeed true that example 4 demonstrates an outstanding stability for diazepam conferred by the MCT oil in combination with the three emulsifiers of claim 1. This result, however, cannot be extrapolated to **any** hydrophobic drugs, particularly when they are chemically and structurally very remote as in the present case, since their negative influence on the

stability of the emulsions differs broadly depending on their chemical properties. Accordingly, the effect achieved in the case of the emulsions containing amphotericin B over document (3) has to be assessed in the light of the available data. As a consequence, the Board notes that no improvement over the stability of the amphotericin B emulsions of (3) can be deduced when comparing the data disclosed in said document (ie at least 10 weeks (example 4) and at least 170 days (figure (4)) with those of the patent in suit (at least 3 months in example 9 and figure 4).

The solution of the problem by the patent in suit has therefore no surprising effect as far as amphotericin B as the hydrophobic drug is concerned.

In view of the foregoing the Board can only conclude that the subject-matter of claim 1 of the set of claims of the main request for the Contracting States other than ES and GR does not involve an inventive step as required by Article 56 EPC since it encompasses at least one non inventive embodiment.

The same findings apply to the subject-matter of claim 1 of the set of claims for the Contracting States ES and GR, which encompasses a usual and obvious process for the preparation of the non inventive emulsion discussed above. The respondent did not submit any additional arguments regarding the claimed process.

#### 4.2 First and second auxiliary requests

The findings under 4.1 also hold good for these two requests as the embodiments with the hydrophobic drug



amphotericin B discussed above are still part of their claim 1.

#### 4.3 Third auxiliary request

- 4.3.1 The subject-matter of this request is restricted to pharmaceutical compositions containing benzodiazepines being in the form of oil-in-water emulsions. According to the description of the patent in suit these emulsions should remain stable during prolonged storage (page 2, lines 32 to 35, page 4, lines 6 to 13).

Document (1) relates also to pharmaceutical compositions of hydrophobic drugs, such as diazepam, being in the form of oil-in-water emulsions (claim 1 and page 5, line 19 up to page 6, line 2).

The Board agrees with the parties that document (1) represents the closest prior art.

- 4.3.2 This document describes oil-in-water emulsion systems containing hydrophobic drugs in medium chain triglycerides (MCT) as an oily carrier and a phospholipid **or** a non-ionic surfactant (page 4, lines 4 to 9 and examples).

According to the description, sodium salts of fatty acids (ie an ionic surfactant) can also be added alternatively as a emulsifier (page 4, lines 4 to 9).

Document (1) does not mention cholic acid and deoxycholic acid.

The problem to be solved as against document (1) can be

seen as the provision of compositions of the oil-in-water type emulsions containing hydrophobic drugs of the benzodiazepine family having improved stability during prolonged storage.

- 4.3.3 This problem is solved by the emulsifier system defined in claim 1.

According to examples 3 and 4 of the patent in suit, a stability of at least 14 months for the emulsions of the drug diazepam can be achieved.

Moreover, the results of the comparative tests of example 5 demonstrate that these effects can only be achieved when the MCT oily carrier is used in combination with the three emulsifiers of claim 1 of the patent in suit.

In addition, the comparative tests of example 5 of the contested patent are closer to the subject-matter of claim 1 than the examples of document (1).

Therefore, in the light of working examples of the patent in suit, the Board is satisfied that the problem has been solved

- 4.3.4 Thus, the question to be answered is whether the proposed solution, ie where the use of a specific emulsifier combination of phospholipids, non-ionic surfactant and cholic acid or deoxycholic acid in the amount as indicated in claim 1, was obvious to the skilled person in the light of the prior art.

Although document (1) discloses the use of a medium

chain triglyceride oil carrier for the preparation of the emulsions as well as two of the emulsifiers of claim 1 of the patent in suit in combination with hydrophobic drugs, this document is silent both about the use of a combination of these emulsifiers for the preparation of oil-in-water emulsions and about the use of cholic acid or deoxycholic acid as ionic emulsifiers.

Having regard to document (2), a review article referring to fat emulsions for intravenous application, the skilled person is taught that the use of a combination of phospholipids and non-ionic surfactants improves the stability of oil-in-water emulsions (page 151, left column, lines 12 to 16).

The skilled person would therefore envisage a combination of a phospholipid and a non-ionic surfactant in order to improve the stability of a diazepam emulsion according to document (1).

It remains therefore to consider whether the addition of the specific ionic surfactants cholic and deoxycholic acid was obvious to the skilled person in order to achieve an improved stability in prolonged storage.

In that respect, document (2) discloses bile salts as surfactants producing excellent emulsions as regards transparency. This document is however silent about any possible improvement in the stability of emulsions to which bile salts are added.

Therefore, the Board is satisfied that the skilled

person faced with the problem of providing an oil-in-water type emulsion for benzodiazepines with improved stability in prolonged storage would not use the unique combination of the three emulsifiers according to claim 1 of the patent in suit.

- 4.3.5 The appellant's objections have been removed by the subject-matter of the claims of the third auxiliary request filed by the respondent during oral proceedings.

In view of the foregoing the Board judges that the subject-matter of claim 1 and of its dependent claims of the set of claims of the third auxiliary request for the Contracting States other than ES and GR involves an inventive step as required by Article 56 EPC.

The same findings apply to the subject-matter of the claim directed to a process for preparing the above discussed emulsions and to the subject-matter of the set of claims for the Contracting States ES and GR as its independent claim 1 is identical to the process claim of the set of claims for the Contracting States other than ES and GR.

## **Order**

### **For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The patent is maintained on the basis of the Third

Auxiliary Request and the description to be adapted thereto.

The Registrar:

The Chairman:

M. Dainese

U. Oswald